Remarks

Applicants have addressed each issue in turn and, for clarity, have provided a heading for each issue. Applicants appreciate entrance of the amendments filed January 24, 2003, Paper #23, canceling claims 1-76 and adding new claims 77-95. Applicants herein cancel claims 78-95. Thus, only claim 77 which reads on the invention previously elected (canceled claims 1-16) is currently pending in the application.

Information Disclosure Statement

The Examiner indicates that the references disclosed in the Information Disclosure Statement filed on 1/23/03 were not considered because copies of the references were not provided. A copy of each of the references on compact disc was also filed on 1/23/03 but was lost or damaged. A replacement copy of the compact disc containing a copy of each of the references was filed on May 7, 2003. A hard copy of each of the references cited in the IDS was also provided to Supervisory Primary Examiner Gary Jones as an "Affymetrix Array IDS binder" for the availability of all Examiners. Applicants believe that the Examiner should now be able to consider each of these references.

Specification

Applicants respectfully request reconsideration of the objection to the specification as amended in Paper No. 22, filed November 26, 2002. The original text as filed used SEQ ID No: 34 as an example target sequence and included the sense match, sense mismatch, antisense match, and antisense mismatch sequences for SEQ ID No. 34. The amendment filed November 26, 2002, Paper No. 22, was intended to shorten the example sequences to include only the

central 9 nucleotides of the original sequences so that each contains less than ten nucleotides and is therefore not required to be within the sequence listing or CRF as provided in 37 C.F.R. 1.821-1.825. However, new typographical errors were introduced into the sequences by that amendment. These errors included deletion of a nucleotide in the example sequence (position 6 of the shortened sequence or position 14 of the original sequence). This error was subsequently translated into each of the example sequences. The orientation of two of the sequences was also reversed in the amendment. The present amendment uses the central 9 nucleotides from SEQ ID No. 34 as an example of a target and provides the sense match, sense mismatch, antisense match and antisense mismatch probes that correspond to the example sequence. The sequences are each listed in the 5' to 3' orientation and this is indicated. Support for the amended example sequences may be found in the specification as filed on page 7, lines 11-19. Additional support for the perfect or sense match probe example may be found in the specification on page 4 lines 19-22 and additional support for the mismatch examples may be found in the specification on page 5, lines 3-16. The shorter sequences convey the same information as the originally filed example sequences. Applicants therefore believe that the shorter sequences in the present amendment do not contain new matter.

Claim Rejections – 35 U.S.C. §§ 101 and 112

Applicants respectfully traverse Examiner's rejection of claims 77 in light of 35 U.S.C. §101 and §112, 1st paragraph. The Examiner has asserted that the array of claim 77 has neither an asserted specific utility nor a well established utility. Applicants respectfully disagree with both of these assertions and believe that the claim is supported by both a specific asserted utility

and a well established utility and that use of the invention by microarray researchers demonstrates that one skilled in the art would clearly known how to use the claimed invention.

A. 35 U.S.C. § 101

On page 4 of the Office Action the Examiner asserts that the use of the array to compare samples by comparing hybridization patterns is "not deemed specific" and on page 5 that the utility is not substantial, citing an "absence of a specific connection between the samples tested and the microarray used". Applicants respectfully disagree, the array clearly has a specific utility as a research tool to analyze a specific set of nucleic acids. The array of claim 77, like an HPLC machine, is a piece of equipment designed and built for a particular use: the analysis of a specific set of nucleic acids (6500 specific murine genes) with a specific set of probes that are complementary to those nucleic acids (SEQ ID Nos. 1-127,811).

The array comprises probes that are specific for a collection of approximately 6500 mouse genes and may be used to obtain a reproducible measurement of which of these nucleic acids are present in a particular sample based on hybridization of the nucleic acids to the probes of the array. The array is particularly useful for making comparisons between two or more experimental samples. An expression pattern can be obtained for each sample and a pair-wise comparison of each of the genes may be used to identify genes that are differentially expressed between two or more samples. Because the array allows a researcher to analyze many genes in parallel and to analyze the same genes using the same probes from multiple samples, the array may be used to generate a signature for the collection of 6500 genes that is characteristic of a particular sample or sample type.

The Examiner indicates that "any array with any cDNAs thereon can be used to compare the gene expression pattern through hybridization patterns for any sample." Applicants assert

that other arrays would be useful for analysis of other genes and other collections of genes, for example from other organisms, but this array is designed and calibrated for the genes in this collection and for the probes of this array. The array of claim 77 is useful for comparing the gene expression pattern of the 6500 mouse genes that are complementary to the probes of the array and not any array with any cDNAs thereon can be used to analyze this specific collection of genes. In addition a researcher would expect that much less information would be obtained if, for example, a sample derived from yeast was hybridized to the array of claim 77.

Applicants would also like to point out that many researchers have used the array of claim 77 to answer research questions, thus demonstrating that one skilled in the art clearly does know how to use the claimed invention to obtain information with real world value. The array of claim 77 was available from Affymetrix, Inc. as a commercial product, the Murine 6500 array, from January 1998 to March 2000. Customers purchased and used the array to generate gene expression profiles from mouse cells under numerous experimental conditions. Applicants have included a list of 19 peer reviewed publications resulting from the use of the Murine 6500 array, see Appendix A. Each reference is summarized briefly in Appendix A and a copy of each reference has been included for the Examiner's convenience. In each of these studies comparison of gene expression profiles from different experimental conditions was used to identify genes whose expression changed from one experimental condition to another. These genes were identified directly from the expression profiles and provided the user with valuable information about how cells respond to different experimental conditions. In some examples, groups of related genes and genetic pathways were identified from the gene expression profiles.

Each of the references listed in Appendix A represents an instance where a researcher has found an application for the array product which is claimed in claim 77, making it clear that a

person of ordinary skill in the art would immediately appreciate why the invention is useful. In each of these references the array was used for a particular practical purpose that resulted in the generation of useful information. In each of the references, researchers used the claimed array to identify changes in gene expression levels between different samples for the approximately 6500 murine genes that are recognized by the probes of the array, illustrating multiple examples of a specific nexus between particular samples and the claimed array. Researchers selected this specific array and not another arrays because this array can be used for massively parallel analysis of gene expression for a specific collection of murine genes. It is clear that the resulting gene expression pattern provides intrinsically useful information of real world significance to a researcher.

B. 35 U.S.C. §112, first paragraph.

Applicants respectfully traverse Examiner's rejection of claim 77 under 35 U.S.C. §112, first paragraph. Applicants believe one skilled in the art would clearly know how to make and use the claimed invention as the Application has specific asserted utility and a well-established utility as indicated in the above response and by the peer reviewed publications in Appendix A.

Objections (Warning)

Applicants have canceled claims 78-81 herein making the objection moot.

Conclusion

For these reasons, Applicants believe all pending claims are now in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5768.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Respectfully submitted,

Date: July 16, 2003

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Appendix A:

1. **Conrad C. Bluel and Thomas Boehm**. Laser capture microdissection-based expression profiling identifies PD1-ligand as a target of the nude locus gene product. *Eur. J. Immunol.* 31: 2497-2503, 2001. The researchers isolated RNA populations of wild-type and nude thymic anlagen from embryos and compared them by gene expression profiling on microarrays representing 22,000 transcripts, to identify Whn target genes.

2. **Todd A. Carter et al.** Chipping away at complex behavior: Transcriptome/phenotype correlations in the mouse brain. *Physiology & Behavior* 73: 849-857, 2001. This article reviews how gene expression profiling in various brain regions of inbred mouse strains has been used to identify genes that may contribute to strain-specific phenotypes.

3. **Aude M. Fahrer et al.** Attributes of γδ intraepithelial lymphocytes as suggested by their transcriptional profile. *PNAS* 98:18 10261-10266, 2001. DNA microarrays were used to study the gene expression profile of γδ IELs in a *Yersinia* infection system to better define their roles.

4. **T. Garcia et al.** Behavior of Osteoblast, Adipocyte, and Myoblast Markers in Genome-wide Expression Analysis of Mouse Calvaria Primary Osteoblasts *In Vitro*. *Bone* 31:1, 205-211, 2002. Researchers implemented a genome-wide analysis by determining changes in expression levels of 27,000 genes during in vitro differentiation of primary osteoblasts isolated from mouse calvaria. Researchers also demonstrate that new array technologies constitute powerful tools to monitor the transcription of genes involved in osteoblastic differentiation.

5. **Richard Glynne et al**. B-lymphocyte quiescence, tolerance and activation as viewed by global gene expression profiling on microarrays. *Immunological Reviews* 176: 216-246, 2000. Global gene expression profiling on DNA microarrays is used to explore the decision between quiescence, tolerance by anergy and activation in splenic B cells.

6. **Carrie R. Graveel et al.** Expression profiling and identification of novel genes in hepatocellular carcinomas. *Oncogene* 20: 2704-2712, 2001. Researchers have performed gene expression profiling of normal and neoplastic livers in C3H/HeJ mice treated with diethylnitrosamine, specifically comparing gene expression in liver tumors to three different states of the normal liver: quiescent adult, regenerating adult, and newborn.

7. **Francine M. Gregoire et al**. Diet-induced obesity and hepatic gene expression alterations in C57BL/6J and ICAM-1-deficient mice. *Am J Physiol Endocrinol Metab* 282: E703-713, 2002. Liver gene expression was analyzed at three time points using Affymetrix GeneChips to better understand the early differential response to the diet.

8. **Bin He et al.** Analysis of gene expression induced by irritant and sensitizing chemicals using oligonucleotide arrays. *International Immunopharmacology* 1: 867-879, 2001. In this study, gene expression induced by toluene diisocyanate, oxazolone, or nonanoic acid was investigated using gene arrays.

9. **K. Hiratsuka et al**. Microarray Analysis of Gene Expression Changes in Aging Mouse Submandibular Gland. *J Dent Res* 81:10 679-682, 2002. High-density oligonucleotide arrays were used to monitor the changes of gene expression levels in the submandibular gland by comparing adult mice with elderly adult mice.

10. **Reinhard Hoffman et al.** Changes in Gene Expression Profiles in Developing B Cells of Murine Bone Marrow. *Genome Research* 12: 98-111, 2002. Gene expression profiles of five consecutive stages of mouse B cell development were generated with high-density oligonucleotide arrays.

11. **Seiichi Ishida et al.** Role of E2F in Control of Both DNA Replication and Mitotic Functions as Revealed from DNA Microarray Analysis. *Molecular and Cellular Biology* 21:14, 4684-4699, 2001. High-density microarrays were used to provide an analysis of gene regulation during the mammalian cell cycle and the role of E2F in this process.

12. **Naftali Kaminski, et al.** Use of Oligonucleotide Arrays to Analyze Drug Toxicity. *Annals New York Academy of Sciences*, 1-8. (2000) Oligonucleotide arrays are useful in the comparison of transcriptional responses in animals susceptible to drug-induced disease with those of genetically modified animals that are resistant to this effect.

13. **Stephen R. Master et al.** Functional Microarray Analysis of Mammary Organogenesis Reveals a Developmental Role in Adaptive Thermogenesis. *Molecular Endocrinology* 16:6, 1185-1203, 2002. DNA microarrays were used to study murine mammary gland development via identification of biologically relevant patterns of gene expression.

14. **Tomas A. Prolla**. DNA Microarray Analysis of the Aging Brain. *Chem. Senses* 27: 299-306, 2002. High-density oligonucleotide arrays were used to provide data on 6347 genes to define transcriptional patterns in two brain regions to examine molecular events associated with brain aging and its retardation by caloric restriction.

15. **H. Shimada et al.** Potential involvement of the AML1-MTG8 fusion protein in the granulocytic maturation characteristic of the t(8;21) acute myelogenous leukemia revealed by microarray analysis. *Leukemia* 16: 874-885, 2002. Oligonucleotide microarrays were used to elucidate the role of AML1-MTG8 in leukemogenesis, by detecting alterations in gene expression caused by ectopic expression of AML1-MTG8 in a murine myeloid progenitor cell line.

16. **Andrew I. Su et al.** Gene expression during the priming phase of liver regeneration after partial hepatectomy in mice. *PNAS* 99:17, 11181-11186, 2002. High-density microarrays were used to examine the gene expression program in the livers of mice after partial hepatectomy to help reveal how regenerative processes are initiated and controlled, as well as to shed new light on processes that lead to liver disease.

17. **T. Kent Teague et al.** Activation changes the spectrum but not the diversity of genes expressed by T cells. *PNAS* 96:22 12691-12696, 1999. Affymetrix gene arrays were used to examine the patterns of genes expressed in resting T cells and T cells 8 and 48 hours after activation to determine if during activation T cells change their patterns of gene expression.

18. **Ruben Zamora et al.** A DNA microarray study of nitric oxide-induced genes in mouse hepatocytes: implications for hepatic heme oxygenase-1 expression in ischemia/reperfusion. *Nitric Oxide* 7: 165-186. Gene array analysis on nitric oxide naïve cells was used to examine changes in nitric oxide mediated gene expression.

19. **Guichao Zeng et al.** Variations in gene expression patterns correlated with phenotype of F-11 tumor cells whose expression of GD3-synthase is suppressed. *Cancer Letters* 178: 91-98, 2002. Gene expression profiles of GD3-suppressed F-11

cells and the control F-11 cells using DNA microarrays were used to identify genes whose expression is correlated with the decreased level of ganglioside GD3